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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GABEL, GAILENE	
ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 12/04/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application No.	Applicant(s)	
	09/485,005	WANKER ET AL.	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims Under Examination

1. Claims 1-25 are pending and under examination.

Trademark Usage

2. The use of the trademark "Triton X-100" has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Drawings

3. This application has been filed with informal drawings which are acceptable for examination purposes only. The drawings in this application are also objected to by the Draftsperson (see PTO-948 attached). Correction is required. However, formal correction of noted defect can be deferred until application is allowed by the examiner.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. Specifically, after contacting the filter with a material suspected of having the amyloid-like fibrils or protein aggregates in step a), it appears that a step would have been performed so as to cause the fibrils or aggregates to be "retained" (and not to include the detergent- or urea- soluble materials).

Claim 1 is incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted element is a label or a tag or a signal producing system to enable detection of amyloid-like fibrils or protein aggregates.

Claim 2 is ambiguous in reciting, "said amyloid-like fibrils or protein aggregates are indicative of a disease" because it does not specifically define how the "amyloid-like fibrils or protein aggregates" are detected so as to be indicative of a disease. See also claim 3.

Claim 4 is ambiguous in reciting, "said disease is associated with a polyglutamine expansion" because it is unclear what is encompassed by the term "associated" as recited in the claim.

Claim 5 is indefinite in reciting "BSE". Acronyms or abbreviations must be recited at least one time in a set of claims.

Claim 6 is vague, confusing, and inconsistent in relation to claim 1 from which it depends in using a same term, i.e. material, to make reference to different components in each claim. For example, claim 1 uses the term "material" to refer to a sample that comprises amyloid-like fibrils or protein aggregates. Claim 6 uses the term "material" to make reference to the filter. Accordingly, claim 6 lacks clear antecedent support in reciting, "material". See also claim 7.

Claim 8 is vague, confusing, and inconsistent in relation to claim 1 or 6 or 7 from which it depends in using a same term, i.e. material, to make reference to different components in each claim. For example, claim 1 uses the term "material" to refer to a sample that comprises amyloid-like fibrils or protein aggregates. Claims 6 and 7 uses the term "material" to make reference to the filter. Claim 8 appears to make reference to "material" that is detergent- or urea soluble. Accordingly, claim 8 lacks clear antecedent support in reciting, "material". See also claim 9.

Claim 9 is confusing in reciting, "material is simultaneously with ... step a), sucked through said filter". Please clarify.

Claim 10 is indefinite for using parenthetical symbols because it is unclear whether the limitations within the parentheses are a part of the claimed invention.

Claim 10 is indefinite in reciting, "a fragment or a derivative thereof" because it is unclear what Applicant intends to encompass in using the terms "fragments" and "derivative" as recited in the claim.

Claim 12 lacks clear antecedent support in reciting, "said material" since the term "material" has been recited to make reference to multiple different components in different claims of the method.

Claim 12 is confusing in relation to claims 1-5 from which it alternatively depends from because it is unclear how the presence of amyloid-like fibrils and protein aggregates are indicative of "human disease" if the "material" is derived from bacteria, yeast, plant, insect, animal, etc.

Claim 13 is indefinite for using parenthetical symbols because it is unclear whether the limitations within the parentheses are a part of the claimed invention.

Regarding claim 13, "and/or" renders the claim indefinite because it is unclear how the limitation following the phrase is part of the claimed invention.

Claim 13, step a') is indefinite in reciting, "incubating ..." without reciting specific requirements to this incubating step. Specifically, the limitations set forth in claim 13 appear to define requirements of the claimed "fusion protein".

Claim 13, step a") is vague and indefinite in reciting, "a compound that induces cleavage at said cleavage site" because it appears to be related to the "suspected inhibitor" recited in step a') but is not clearly defined and recited as such.

Claim 14 is ambiguous in reciting, "site cleavable by intein self-cleavage". Please clarify.

Claim 15 is confusing in reciting, "inhibitor of said compound that induces cleavage" because the compound in claim 13, step a") from which it depends appears to be the inhibitor defined in claim 13, step a'). Please clarify.

Claim 16 is indefinite for using parenthetical symbols because it is unclear whether the limitations within the parentheses are a part of the claimed invention.

Claim 18 lacks clear antecedent support in reciting, "said material" since the term "material" has been recited to make reference to multiple different components in different claims of the method.

Claim 20 is indefinite in reciting "SDS". Acronyms or abbreviations must be recited at least one time in a set of claims.

Claim 20 is indefinite in reciting the trademark "Triton X-100" without capitalizing it. See paragraph no. 2.

The same analogous comments and rejections in claim 15 apply to claims 21-23 and 25 in reference to the "compound" and the "inhibitor". Please clarify.

Claim 23 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim must be recited in the alternative only. See MPEP § 608.01(n). However, in an effort to shorten prosecution of the instant application, claim 23 has been treated on the merits.

Regarding claim 23, "and/or" renders the claim indefinite because it is unclear how the limitation following the phrase is part of the claimed invention.

Claim 24 has improper antecedent basis problem in reciting, "a fusion protein as defined in ...".

Claim 25 has improper antecedent basis problem in reciting, "a filter as defined in...".

Claim 25 has improper antecedent basis problem in reciting, "a compound ... as defined in ...".

Claim 25 has improper antecedent basis problem in reciting, "an inhibitor as defined in ...".

Claim 25 lacks clear antecedent support in reciting, "said compound of c)".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-3, 5-12, and 18-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Tateishi et al (Membrane, 1993).

Tateishi et al. teach a method of detecting and removing detergent insoluble amyloid-like fibrils or protein aggregates (prion protein or PrPCJD) from the brain sample of mice with spongiform encephalopathy using a filter (virus removal membrane) which is cuprammonium regenerated cellulose hollow fiber (see Abstract and page 358, column 1). Filters for use in protein aggregate removal are commercially known with different mean pore sizes ranging from 35 nm to 75 nm (see page 358, column 2). Filtration is carried out under constant transmembrane pressure of 180 mmHg at 20 C. The existence of detergent insoluble amyloid-like fibrils or protein aggregates indicative of the neurodegenerative disease (agent infectivity) is confirmed by treatment with a

detergent (surfactant), i.e. Sarkosyl (see page 361, column 2). The presence of PrPCJD protein in the filter is detected immunohistchemically using a chemical reagent (see page 359, column 2).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 4 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tateishi et al (Membrane, 1993) in view of Trottler (Nature, 1995) and Stott et al. (Proc. Natl. Acad. Sci. USA, 1995).

Tateishi et al. has been discussed supra. Tateishi et al. differ in failing to teach that the neurodegenerative diseases are associated with a polygutamine expansion.

Trottler et al. teach neurodegenerative diseases such as in Huntington's disease which are associated with polyglutamine expansion of specific proteins. Trottler et al. teach that pathological threshold for these proteins is 37-40 glutamine expansion whereas the corresponding normal proteins contain polymorphic repeats of up to 35 glutamines (see Abstract). Trottler et al. characterize monoclonal antibodies that selectively recognize polyglutamine expansion in proteins and use them to detect presence of polyglutamine stretch on Western Blot (see page 403, column 1).

Stott et al. teach that some transcription factors and proteins contain polyglutamine repeats and their abnormal expansion is linked to neurodegenerative diseases. Stott et al. teach that polyglutamine forms B-strands which are held together by hydrogen bonds between their amide groups, thus, forming polar zippers. Multiplicity of hydrogen bonds between extended strands of glutamine repeats in an oligomer increases stability of these proteins (see page 6509). Stott et al. teach that pathological effects and abberant transcriptional activity arise when expanded glutamine repeats cause proteins to acquire excessively high affinities for each other or for complementary regulatory proteins with glutamine repeats (see page 6512).

One of ordinary skill in the art at the time of the instant invention would have reasonable expectation of success in detecting proteins with polyglutamine expansion in the teaching of both Trottler and Stott using the method and device of Tateishi which utilizes cuprammonium regenerated cellulose hollow fiber in acquiring and detecting insoluble amyloid-like fibrils and protein aggregates because Stott specifically taught that proteins with polyglutamine expansion have excessively high affinities with each

other; thus, providing stability and insolubility to certain protein aggregates and Tateishi specifically taught application of his method for capture and detection of such insoluble protein aggregate forms.

7. Claims 13-14, 16, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tateishi et al (Membrane, 1993) in view of Smith (EP 0 293 249) and Stott et al. (Proc. Natl. Acad. Sci. USA, 1995).

Tateishi et al. has been discussed supra. Tateishi et al. differ in failing to teach a fusion protein as described in claim 13.

Smith discloses a fusion protein comprising an amyloidogenic polypeptide (foreign protein or peptide) that aggregates into amyloid-like fibrils or protein aggregates fused with a polypeptide (glutathione-S- transferase) that enhances solubility or prevents aggregation. An enzymatically cleavable link is preferably provided in the fusion protein between the glutathione-S-transferase and the insoluble foreign protein (see Abstract and columns 3 and 5). Smith teaches that insoluble or partially soluble fusion proteins can be purified by affinity chromatography if they are solubilized in a solubilizing agent which does not disrupt binding to glutathione agarose such as Triton X-100 or dithiothreitol. Insolubility has been associated with increased protein stability (see column 4).

Stott et al. has been discussed supra.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to detect the presence of detergent or urea insoluble amyloid-like fibrils

such as taught by Tateishi in a partially or wholly insoluble fusion protein such as taught by Smith because Tateishi specifically taught application of his method for capture and detection of insoluble protein aggregate forms including those manifested in neurodegenerative diseases in the teaching of Stott and the fusion protein specifically described and characterized by Smith as being in insoluble or partially soluble form.

8. Claims 15 and 21-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tateishi et al (Membrane, 1993) in view of Smith (EP 0 293 249) and Stott et al. (Proc. Natl. Acad. Sci. USA, 1995) as applied to claims 13-14, 16, and 20 above, and further in view of Vitck et al. (US 5,935,927).

Tateishi et al., Smith, and Stott et al. have been discussed supra. Tateishi et al., Smith, and Stott et al. differ in failing to teach an inhibitor of amyloid-like fibril or protein aggregate formation.

Vitck et al. disclose that advanced glycosylation end-products (AGE)- amyloid polypeptides, i.e. AGE-β amyloid peptide (βAP) facilitate aggregation of amyloid fibrils in neurodegenerative diseases such as Alzeimer's disease (see column 5, lines 42-64, columns 9 and 11). Further, Vitck et al. disclose treatment of neurodegenerative disease using pharmaceutical compositions comprising inhibitors that prevent formation or cross-linking of AGE proteins resulting to amyloidosis and formation of amyloid fibrils (see columns 13-15).

One of ordinary skill in the art at the time of the instant invention would have been motivated to inhibit formation of amyloid fibrils in neurodegenerative diseases

such as in the teaching of Tateishi, Smith, and Stott using inhibitors in the form of pharmaceutical compositions such as taught by Vitck because Vitck specifically taught that such inhibitors prevent facilitated aggregation of amyloid fibrils in neurodegenerative diseases such as set forth in the claimed invention.

9. No claims are allowed.

Remarks

10. Prior art made of record are not relied upon but considered pertinent to the applicants' disclosure:

Perutz (Current Opinion in Structural Biology, 1996) discusses glutamine repeats in inherited neurodegenerative diseases.

Serban et al. (EP 0 206 302) disclose immunological analysis of amyloid proteins based on the efficient binding of the proteins to plastic surface such as nitrocellulose or cellulose acetate (see Abstract and page 4).

Burke et al. (US 5,723,301) disclose that glyceraldehydes-3-phosphate dehydrogenase (GAPDH) binds to expanded polyglutamine regions of proteins and synthetic peptides which are found in neurodegenerative diseases (see column 1). Vitck et al. further disclose a compound which inhibits binding of GAPDH to the polyglutamine region (see column 2 and 4).

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday-Thursday from 6:30 AM - 4:00 PM and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (703) 308-3399. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gailene R. Gabel
November 24, 2001

LONG V. LE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600
11/30/01